

**REMARKS****Claim Amendment**

Claims 1 and 11 have been objected to due to a typographical error. The error has now been corrected. Claims 1 and 11 now recite “wherein prior knowledge of the datapoints to be clustered is not necessary.”

New Claim 19 is Claim 8 written in independent form.

This amendment introduces no new matter.

**Interview Summary**

A telephonic interview with the Examiner took place on November 19, 2003. Examiner Shubo Zhou, Ph.D. and Examiner John Brasca, Ph.D., representing the U.S. Patent and Trademark Office and MaryLou Waikimura, Esq. and Alex Akhiezer, Ph.D., representing the Applicants, participated. The Applicants thank the Examiner for granting and conducting the interview.

In the course of the interview, the arguments proposed by the Applicants to overcome the rejection of record under 35 U.S.C. §103 over Mack and Mangiameli were discussed. The Applicants presented arguments that neither reference provided motivation to modify the prior art and that expectation of success is not found.

The Examiner stated that the main part of the motivation to combine the cited references comes from Mangiameli rather than Mack. Mangiameli teaches the superiority of SOMs over other clustering algorithms. The Examiner stated that one skilled in the arts of both gene expression analysis and data analysis would be motivated by the teaching of Mangiameli to modify the teaching of Mack.

The Applicants argued that, absent any specific teaching in Mangiameli that the SOMs algorithm is particularly suited for gene expression analysis and in view of total absence of a specific teaching on gene clustering in Mack, one of ordinary skill cannot have an expectation of success. The Applicants further argued that, absent such expectation, combining Mack and Mangiameli indicates impermissible hindsight.

The Examiner and the Applicants were unable to reach agreement during the interview.

The Examiner stated that he was removing finality of the Office Action mailed on October 1, 2003 (Paper No. 32) and issuing a supplementary action (Paper No. 33). The Examiner further stated that no claims were allowable at this time.

Applicants now respond to the Office Action at hand (Paper No. 33).

#### Rejection of Claims 1 - 18 Under 35 U.S.C. § 103 (a)

##### 1. Summary of the Examiner's Rejection

The Office Action rejects Claims 1-18 as being unpatentable under 35 U.S.C. § 103 (a) over U.S. Patent No. 6,303,301 to Mack in view of Mangiameli *et al.* (European J. Operational Research, Sept. 1996, Vol. 93, pgs. 402-417). The Office Action states that Mack's method "comprises receiving gene expression values of datapoints, clustering the datapoints, and providing output display indicating the cluster of the datapoints." The Office Action states that Mack does not explicitly disclose clustering using SOMs.

The Office Action states that Mangiameli *et al.* applied the SOM method as well as seven other hierarchical methods of clustering to multiple data sets with real-world data imperfections and concluded that SOM is superior to the other clustering methods.

The Office Action further states that the fact that Mangiameli *et al.* compared SOM to other clustering methods indicates that SOM is an art recognized equivalent of other clustering methods. The Office Action concludes that, since Mangiameli *et al.* demonstrated superiority of SOM for data analysis, one of ordinary skill in the art would have been motivated to modify Mack to use SOM for gene expression data. The Office Action also states that there would have been a reasonable expectation of success of modifying Mack with the teaching of Mangiameli *et al.* because Mangiameli *et al.* used data derived from various sources.

##### 2. The Combination of Mack and Mangiameli *et al.* Does Not Result in Applicants' Invention

The Applicants respectfully disagree that the combination of Mack and Mangiameli *et al.* results in the instant invention.

The instant invention discloses and claims a **method for clustering** a series of gene expression values. This method uses SOMs for clustering and is, therefore, an unsupervised and

“no-prior-knowledge-required” method. Specifically, it *creates categories* of the classified objects (here, genes).

Mack discloses methods of “decipher[ing] the complex regulatory relationship among genes” (column 1, line 67 to column 2, line 1). Mack explains (see Figure 2 and column 2, 2<sup>nd</sup> full paragraph) that it is a two-step process: first (i) a cluster map is created and then (ii) a regulatory pathway map (“causal model”) is generated using statistical analysis. The Examiner also acknowledges that “clustering” is a separate step from “causal model”, page 4 of the Office Action mailed on February 11, 2003.

The Applicants submit that, even if Mack and Mangiameli are combined, the result will be *a method of determining causal models using SOMs*, not a method of clustering a series of gene expression values as required by Claim 1 of the instant application.

Not only is a method of determining causal models using SOMs *not* the applicant’s claimed invention, but, in fact, one skilled in the art cannot have expected that such combination would be successful since Mack does not disclose or suggest SOM or other alternatives for the clustering step, but mentions generally that other causal model methods are appropriate for the causal model step (Column 28). On the other hand, Mangiameli *et al.* does not suggest that SOMs could be used for gene expression analysis or for analyzing causal models.

### 3. No Motivation to Combine Mack and Mangiameli

As noted before in the Declaration under 37 C.F.R. 1.132 by Kreiman, (section 7, page 3), Mack does not disclose how, specifically, clustering is accomplished. Indeed, Mack references several books on the general subject of statistical analysis of data and then proceeds to discuss a preferred method for the testing and building of causal models: LISREL. (Mack, column 27, line 48 to column 28, line 2)

It is in this discussion of preferred methods of *generating a causal model*, the second step of Mack’s method, which is independent of the clustering step, that Mack states that “other causal model methods are also appropriate.” (Column 28, 2<sup>nd</sup> paragraph).

The Applicants submit that one skilled in the art would *not* have been motivated by this suggestion in Mack (that other statistical methods for generating causal models can be used to accomplish the second step of his method) to modify the first step of his method (i.e., clustering)

with the teaching of Mangiameli *et al.* The Declaration by Kreiman is evidence of such lack of motivation in the cited references, to one of ordinary skill in the art.

The Applicants further submit that one skilled in the art would certainly not consider it obvious to modify the teachings of Mangiameli *et al.* a highly technical text on Mathematical Statistics, to accomplish gene expression analysis as in the claimed invention.

To summarize, neither Mangiameli *et al.* nor Mack nor any other art of record teach or suggest that the SOM method can be successfully applied to gene expression analysis as in the claimed invention.

#### 4. Applicants' Amendment

To further emphasize the foregoing patentable distinctions of the present invention method of clustering gene expression values over Mack's method of deciphering regulation relationship among genes, new Claim 19 is presented. New Claim 19 essentially is Claim 8 written in independent form. Thus no new matter is introduced.

If new Claim 19 is found to be allowable, Applicants propose to make Claims 2-7 and 9-10 depend from Claim 19.

Claim 16 may similarly be rewritten in independent form with Claims 12-15 and 17-18 made dependent therefrom.

Applicants propose the foregoing and ask for acceptance by the Examiner in order to move prosecution of the subject application forward in good faith. The claims as presented and proposed recite the present invention in terms that are novel and not made obvious by the cited art. Thus the §103 rejection is believed to be overcome and should be removed.

**CONCLUSION**

In view of the above amendments and remarks, it is believed that all claims (1-19) are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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